PHARMACOLOGICAL AND PHYSIOLOGICAL STUDIES ON PERSPIRATION CENTERS. III. EFFECT OF THE MEDULA OBLONGATA ON SWEAT EXCRETION AND BODY TEMPERATURE

B. Hasama

Translation of "Pharmakologische und physiologische Studien uber die Schweisszentren. III. Mitteilung: Zur Frage nach der Beeinflussung der Schweisssekretion und der Korpertemperatur durch die Medulla oblongata," Archiv fur experimentelle Pathologie und Pharmakologie, Vol. 153, 1930, pp. 257-290

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
WASHINGTON, D.C. 20546 SEPTEMBER 1974

STANDARD TITLE PAGE

1. Report No. NASA TT F-15,898	2. Government Accession No.	3. Recipient's Catalog No.
4. Title and Subtitle PHARMACOLOGICAL AND PHYSIOLOGICAL STUDIES ON PERSPIRATION CENTERS. III. EFFECT OF THE MEDULLA OBLONGATA ON SWEAT EXCRETION AND BODY TEMPERATURE		5. Report Date September 1974 6. Performing Organization Code
7. Author(s) B. Hasama, Pharmacological Institute of the Medical Department, Nagasaki, Japan		8. Performing Organization Report No. 10. Work Unit No.
9. Performing Organization Name and Address Leo Kanner Associates Redwood City California 94063		11. Contract or Grant No. NASw-2481 13. Type of Report and Period Covered Translation
12. Sponsoring Agency Name and Address National Aeronautics and Space Administration, Washington, D.C. 20546		14. Sponsoring Agency Code

15. Supplementary Notes

Translation of "Pharmakologische und physiologische Studien über die Schweisszentren. III. Mitteilung: Zur Frage nach der Beeinflussung der Schweisssekretion und der Körpertemperatur durch die Medulla oblongata," Archiv für experimentelle Pathologie und Pharmakologie, Vol. 153, 1930, pp. 257-290

16. Abstract Injecting acidic Ringer's solution into the carotid or flushing the fourth ventricle with it causes sweat excretion and a temperature rise; alkaline solution inhibits sweat excretion and temperature rise. Elimination of the diencephalon does not change these results. Chemical and electrical stimulation are studied in order to determine the areas of the medulla oblongata which are involved, and ergotoxine and atropine are used to block the sympathetic and parasympathetic systems. The dorsal vagal nucleus is concluded to be a subordinate perspiration and thermoregulatory center made up of a sympathetic part and a parasympathetic part which react differently to chemical, thermal and electrical stimuli, independently of diencephalic centers.

17. Key Words (Selected by Author(s))	18. Distribution Statement
	Unlimited

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price
Unclassified	Unclassified	40	

PHARMACOLOGICAL AND PHYSIOLOGICAL STUDIES ON PERSPIRATION CENTERS. III. EFFECT OF THE MEDULLA OBLONGATA ON SWEAT EXCRETION AND BODY TEMPERATURE

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My earlier articles [1, 2] on the mechanism of the central /257* control of sweat excretion and body temperature have provided a contribution to clarification of the questions associated with this. Interest was then turned to the significance of the medulla oblongata for thermoregulation and sweat excretion. The present article covers this problem as a continuation of the earlier work. In the course of a large number of experimental neurological studies on the vegetative nervous system which we have performed over many years, the significance of the regio subthalamica as a higher vegetative center has become more and more apparent. In consideration of the fact that the same result occurs upon stimulation of the medulla oblongata, particularly the base of the rhomboid fossa, as in the case of diencephalon stimulation, e.g. changes in vasomotor activity, blood sugar level, water budget, salt metabolism and perspiration excretion, it appears justified to also assume a secondary vegetative center of lower order here. In my earlier articles [1, 2], I reported on the interesting observation that a perspiration center exists at the regio subthalamica in the cat which reacts very sensi- /258 tively to thermal, chemical and toxic effects. On the basis of previous observations concerning causal relationships between perspiration excretion and vasomotor activity, whose center, subordinate to the diencephalic center, is known to be localized in the medulla oblongata, it was demonstrated that the perspiration centers exhibit a behavior similar to that of the vasomotor centers. In addition, the evidence that the sudorific nerves

* Numbers in the margin indicate pagination in the foreign text.

possess a histological organization similar to that of the vascular nerves suggested that there is a medullary perspiration center of lower order which would be comparable to the vasomotor center. Now while the existence of a chemically, toxically and thermally excitable perspiration center in the regio subthalamica has been demonstrated, the assumption of a subordinate medullary perspiration center does not at the present time stand on such a well-confirmed experimental foundation. As far as this problem is concerned, the classical experiments in the older literature [3, 4, 5], which indicated the possibility of the induction of sweat excretion by stimulation of the medulla oblongata, took the question of the existence of a medullary perspiration center into consideration. In spite of its great importance, there is so far no conclusive evidence to decide the question of whether the excretion of sweat due to stimulation of the medulla oblongata involves the excitation of perspiration pathways descending from the diencephalon or that of the actual perspiration centers located there. More recent results of experimental neurology suggest that the dorsal vagal nucleus is important as the origin of efferent vegetative fibers. The idea [6] that sugar metabolism is closely connected with the dorsal vagal nucleus induced me to express the hypothesis that the latter also exerted a certain effect on thermoregulation. With regard to sweat excretion, it was pointed out that it is performed in part, at least, via the cells of the dorsal vagal nucleus, which are considered to be medullary centers of smooth musculature or secretory fibers.

It therefore appears to be urgently necessary to go into this question in somewhat greater detail. In order to delimit the zone involved in sweat excretion and thermoregulation in the medulla oblongata, I have primarily stimulated the various regions of the rhomboid fossa thermally.

The chemical regulation of sweat excretion, which becomes apparent, even in superficial observation, in the increased sweat

excretion that accompanies anyincrease in blood venosity, e.g. during suffocation, appears to be no less important. My next task /259 is to delimit the sweat-inducing zone by hematogenic or direct reaction modification of the various areas of the medulla oblongata, with simultaneous monitoring by microscopic examination.

Method

Cats, which are known to be particularly suitable for perspiration studies, were again used as the experimental animals. The method for measuring quantity of perspiration and body temperature is likewise the same as in my earlier articles [2], so details can be dispensed with here. It appears appropriate, however, to briefly describe the method employed to expose the medulla oblongata. Access to the rhomboid fossa was obtained in the conventional manner by removing the membrana atlanto-occipitalis and breaking away the adjacent portion of the planum occipitale and the vertebral arches of the first and second cervical vertebrae. The incision is then made through skin and subcutaneous muscle at the rear surface of the neck along the center line, from the protuberantia occipitalis externa to the upper two or three cervical vertebrae. The long neck muscles are then pushed apart, the margins of the incision are drawn apart with hooks, and the thick spinous process of the second cervical vertebra and the m. spinalis lying on both sides of the vertebral arches are exposed. The latter is separated from the vertebra with a scalpel or a raspatory. The ligament between the arches of the first and second cervical vertebra and then the membrana atlanto-occipitalis are subsequently severed, whereupon the dorsal wall of the spinal canal of the first and second cervical vertebrae and the planum occipitale are broken away with a rongeur. The open spinal canal now lies before us. The fatty tissue which covers the dura is cautiously pushed apart and the latter, along with the arachnoidea, is split longitudinally; we then grasp the severed edges of the meninges, pull them to the

side, and press cautiously. The expelled liquor is soaked up with cotton. After the cisterna subcerebellaris has been opened and the arachnoidea has been torn apart, the rear section of the cerebellum is lifted with fine forceps -- a spatula was used in the first experiments. If the zygapophyses are not broken off, injury to the arteria and vena vertebralis can be avoided, and no bleeding occurs. We now obtain a clear overview of the entire rhomboid fossa. The operation was conducted under rigorously aseptic conditions with light ether anesthesia. These manipulations were tolerated by the cat without visible disturbances in its behavior.

Operation shock after exposure of the oblongata was slight and short-lasting; just 30 min after the operation, the animals were able to sit and run normally. Body temperature was often not reduced at all, or only temporarily by several tenths of a degree by the operation, and usually returned to normal in 30 min. The effect of modifying the reaction of the medulla oblongata on sweat excretion and body temperature was first studied. The experiments were taken in three directions: first, hematogenic reaction modification; secondly, reaction modification from the liquor; and, thirdly, direct reaction modification. In order to establish the effect of hematogenic reaction modification of the medulla oblongata on sweat excretion and body temperature, Ringer's solution with various hydrogen ion concentrations was injected directly into the carotid with a syringe. To produce reaction modification of the medulla oblongata from the liquor, heated Ringer's solution of various pH values was flushed through the fourth ventricle by Beckmann's method [7]. The direct reaction modification of various areas of the medulla oblongata was performed by inserting a fine needle into the various areas, the point of which was wrapped in cotton and dipped in Ringer's solution of various pH. After the puncture experiment, a histological examination was performed at the puncture point in order to precisely observe the location at which the puncture was made.

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In addition, the experiments were extended in two other directions; the effects of thermal stimulation, on one hand, and galvanic stimulation, on the other, of the medulla oblongata on sweat excretion were studied. Additional material on the method used for electrical and thermal stimulation are not necessary here, since I worked with the same method that I described extensively in my earlier article [2]. Only the basic features of the method were described. An article appearing later provides information on details. Most of the experiments were performed in the months of March through May. Room temperature during the experiments was generally 15-23°C.

Experimental Results

1. Effect of Reaction Modification in the Carotid Blood on Sweat Excretion and Body Temperature

Aside from the thermal factors involved in the central stimulation of sweat excretion, it appears very highly probable that a chemical control of sweat excretion also exists, since sweat excretion is known to be triggered by increased blood venosity during suffocation. The close link between the respiratory and perspiration centers is made clear by the occurrence of sweat excretion during thermotachypnea, as well as during accelerated respiration due to suffocation. It is also known that respiration can be regulated from the blood, alone, by a change in the CO_2/O_2 ratio. While chemical regulation of the bulbar centers for respiration and vasomotor functioning through a change in hydrogen ion concentration in the blood has been studied extensively by several authors, little attention has unfortunately been devoted to the effect of reaction modification of the bulbar perspiration centers. We are still very incompletely informed so far on chemical regulation of the bulbar perspiration centers. /261
Nevertheless, we find a few data in the literature on the question of interest to us, chemical control of the perspiration centers.

Luschinger and Nawrocki [8] observed sweat excretion on all four paws of the cat when CO_2 was carried by the blood of the a. carotis and attributed this to stimulation of the perspiration centers in the extended marrow. Dieden's [8] objection to their experiments was that the diencephalon could be stimulated just as well in this manner. In my earlier article [2], it was shown that the direct application of acidic Ringer's solution to the regio subthalamica in the cat produces increased sweat excretion. The purpose of the present study was to establish whether and to what degree a change in sweat excretion and body temperature, in addition to respiratory modification, is possible through reaction modification in the area of the bulbar centers. It was necessary here to have the operant stimulus affect only the bulbar centers if possible and to rule out peripheral effects of this stimulus. An attempt was first made to produce reaction modification in the centers via the blood by the injection of Ringer's solution of various pH into the bloodstream. In all primary hematogenic reaction shifts in the experiment, however, the possibility exists of peripheral effects due to altered blood composition. This was reduced in these experiments by injecting the solution into the carotid blood. It did likewise reach the general circulatory system from here, but appreciable effects on the centers could still be triggered in this manner even with relatively small quantities of liquid, by which the contents of the vascular system would not be markedly affected and which, when injected intravenously, remained almost ineffective. A pressure increase in the carotid was avoided as much as possible. This reaction change in the blood has a secondary effect on the reaction of the tissue, i.e. on the reaction of the centers in this case. For methodological reasons, the reaction in the centers can not yet be measured directly. A possibility had to be found of demonstrating the fact of a reaction modification in the centers, even if by an indirect approach. This was attempted with the aid of simultaneous observation of respiratory motion. But hematogenic reaction modifications do not just

affect the respiratory center, but all bulbar centers, too. The injected liquid was Ringer's solution, which produces various pH values as the result of adding hydrochloric acid or sodium bicarbonate. The pH of the solution was always measured colorimetrically. The intraarterial injection of acidic (pH 2.5) Ringer's solution at body temperature (7 cm^3 within 1 to 2 min in cats weighing 2.5 to 3 kg) produced -- as Table 1 shows -- not only a stimulating effect on the respiratory and vasomotor centers -- accelerated respiration and contraction of the aural vessels -- but also increased sweat excretion on all four paws. Sweat excretion begins just a few minutes after injection, reaches its peak 10 to 15 min after injection, but then drops off gradually and ceases completely about 30 min after injection. We occasionally observe cases in which sweat excretion lasts longer than 1 hour. As far as temperature change is concerned, a rise is always observed. The temperature rise accompanying the intraarterial injection of 7 cm^3 acidic Ringer's solution (pH 2.5) varies individually between 0.5 and 1.4°C and averages 0.8°C. The elevated temperature is maintained for about 40 or 50 min and then slowly drops to the normal level (Table 1). The minimum dose for producing sweat excretion and temperature rise at a pH of 2.5 for the acidic Ringer's solution applied is 3 cm^2. Upon injection into the vena jugularis, on the other hand, even a relatively large quantity of Ringer's solution of the same pH, e.g. 15 cm^3, produces no sweat secretion or temperature rise. The maximum pH which induces the above, if the quantity injected intraarterially is 7 cm^3, is 4. The greater the pH displacement in the acidic direction and the greater the quantity of liquid injected intraarterially, the more intense the effect. This fact raises the question of whether sweat excretion due to a hematogenic acid shift involves excitation of the diencephalon or that of the bulbar centers. I attempted to separate the medulla oblongata from the brain stem in order to ascertain whether the brain stem is involved in this sweat excretion. The medulla oblongata

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was exposed and the occipital squama was then chiseled open to a large extent, without injuring the blood vessels if possible. Part of the cerebellar material was now cautiously removed with a small spoon in order to provide an overview of the peduncles. The exposed peduncles were then severed transversely. In order to avoid heavy bleeding, I ligated the carotid vessels prior to separation. As soon as separation had occurred, body temperature exhibited a gradual drop.

Nevertheless, the intraarterial injection of acidic Ringer's solution (pH 2.5), 7 cm^3, continued to be followed by sweat excretion at all four paws and a temporary rise in temperature occurred, but this began to drop off again about 30 min after injection, as the effect disappeared. Injection was repeated once more with the same results. When alkaline Ringer's solution (pH 9), 7 cm^3, was injected, however, no sweat excretion occurred. Intraarterial injection of the latter produced a decrease in breathing rate and a slight temperature drop, by several tenths of a degree, but no sweat excretion, even if a large quantity, such as 20 cm^3, was used. Gollwitzer-Meier's finding [9] that the intraarterial injection of a solution which increases the blood carbon dioxide concentration causes an increase in respiratory volume and a rise in blood pressure but that the same injection of a solution which reduces carbon dioxide concentration causes a decrease in respiratory volume and a drop in blood pressure has suggested to me that the intraarterial injection of an alkaline solution produces an inhibiting effect on the medullary perspiration center, as it does on the other bulbar centers. In order to check this assumption, I have studied whether alkaline injection suppresses the excretion of sweat caused by the application of heat. The cat was placed in a hot box for the purpose of heating it, the head and hind paws remaining outside the box. Three electric lamps mounted on the wall of the box were used for heating. /261

TABLE 1. EXPERIMENT WITH THE INJECTION OF ACIDIC RINGER'S SOLUTION (pH 2.5), 7 cm3, INTO THE A. CAROTIS. CAT, WEIGHT 2520 g, MALE. AMBIENT TEMPERATURE 17°C

		Before injection	After injection																	Temperature rise, total perspiration
			5	10	15	20	25	30	35	40	45	50	55	60	70	80	90	100	110	120	
			Min.																		
Temp. in °C . . .		37,9	38	38,2	38,2	38,4	38,5	38,7	38,7	38,9	38,9	38,8	38,9	38,9	38,9	38,8	38,6	38,5	38,3	38,1	1,0
Perspiration in mg	right	—	2	4	5	4	3	—	—	—	—	—	—	—	—	—	—	—	—	—	23
	left	—	3	4	6	5	3	2	—	—	—	—	—	—	—	—	—	—	—	—	27

[Note: Commas in numerals are equivalent to decimal points.]

TABLE 2. EXPERIMENT WITH INJECTION OF ALKALINE RINGER'S SOLUTION (pH 9), 7 cm3, INTO THE A. CAROTIS WHILE THE CAT WAS BEING HEATED IN THE BOX. CAT, WEIGHT 2700 g, MALE. AMBIENT TEMPERATURE 16°C

		Before heating	During heating (50°C)															
			Before injection						After injection									
			5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80
			Min.						Min.									
Temp. in °C . . .		37,7	37,7	37,8	37,9	37,9	38	38	38	37,9	37,7	37,7	37,8	37,9	38,1	38,3	38,4	38,4
Perspiration in mg	right	—	3	4	6	5	5	5	2	0	0	0	3	5	5	6	5	5
	left	—	3	4	5	4	6	5	3	0	0	0	2	6	5	5	6	5

Temperature in the box could be determined by means of a thermometer which was inserted through the lid of the box. The temperature was 50°C. During heating in the box, I observed the following reactions in the cat: The cat becomes restless, cries, saliva excretion is conspicuous, the tongue sometimes becomes cyanotic, polypnea occurs, body temperature rises several tenths of a degree upon heating for 30 min, and sweat excretion occurs on the four paws. When increased sweat excretion had commenced on the four paws, I injected alkaline solution (pH 9), 7 cm^3, into the carotid. The injection not only eliminated the thermotachypnea, but also suppressed the excretion of perspiration to a conspicuous degree. Even with a small quantity, such as 3 cm^3 (pH 9), I always observed this inhibiting effect. The larger the quantity injected and the more alkaline the injected solution, the more pronounced the inhibiting action. But if even a relatively large quantity, such as 10 or 20 cm^3, was injected into the vena jugularis, I was unable to observe this effect. The intraarterial injection of alkaline Ringer's solution (pH 9), 7 cm^3, made it /265
possible, as mentioned above, to produce a pronounced inhibition of sweat excretion, temperature rise and tachypnea. Sweat excretion was temporarily suppressed with a steep dropoff to the point of complete disappearance, but sweat excretion began again within 30 min. Injection also reduced the increased temperature to normal with a rapid dropoff, but it began to rise again within 30 min. In order to illustrate the experimental results, let me refer you to Table 2, which shows a typical case.

If the pH of the solution is less than 2.5, sweat excretion and a temperature rise are always observed upon intraarterial injection of 3 cm^3, and if it is greater than 9, inhibition of the two always occurs. The farther the pH of a solution of which 3 cm^3 is injected intraarterially drops below 2.5, the more intense the sweat excretion and temperature rise, and the more it exceeds 9, the more distinctly the two are inhibited.

2. The Effect of Liquor pH Modification upon Sweat Excretion and Body Temperature

It also had to be possible to affect the reaction in the medullary perspiration center by modifying the reaction in the liquor. If carbon dioxide concentration in the liquor increases, the undissociated carbonic acid will diffuse into the bulbar centers and increase their $[H^+]$. It is known, for example, that hyperpnea can be caused by a rise in liquor carbon dioxide concentration, just as by an increase in blood carbon dioxide concentration, likewise through a rise in $[H^+]$ in the respiratory center. Thus in many experiments to date, solutions by which hydrogen ion concentration in the liquor is modified have been injected subdurally or suboccipitally. Recently, Gollwitzer-Meier [9] achieved the same effect on the bulbar centers by the subdural injection of an acidic solution as by intraarterial injection, e.g. increased respiratory volume and blood pressure. Such experimental findings suggested that it would be possible to cause a modification of the reaction of the medullary perspiration center from the liquor. For the time being, however, there is no conclusive experimental evidence available for this assumption. The possibility of causing a modification of the reaction of the medullary perspiration center from the liquor has the advantage that injection into the bloodstream can thereby be completely avoided, thus ruling out all peripheral effects. In place of subdural injection, I applied irrigation in the fourth ventricle by Beckmann's method [7] with Ringer's solutions of various pH values at body temperature, with simultaneous pressure monitoring, in order to avoid an increase in spinal pressure and a resultant effect on the perspiration center. The cat was first tied on its side with the head inclined slightly forward, without the head being rotated in the process. After anesthesia of the skin below the occipital squama with Novocaine, I inserted two lumbar puncture needles, about 4 cm long, 1 cm below the palpable occipital margin on the center line; one of these was used to introduce the solution and

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the other to drain it. The needles were inserted diagonally upward and parallel to one another so that they were certain to hit the descending bony branch of the occipital squama. Once the needles had reached it, they were pushed down farther until they finally reached the margin of the foramen occipitale, where one then distinctly feels the resistance of the membrana atlanto-occipitalis, and this membrane was then carefully penetrated. Once the elastic resistance of the membrane ceases, the needles may not be pushed down farther. The depth to which the needles must be inserted is usually 3 to 3.5 cm in the cat. When one has reached the proper location in the fourth ventricle, some liquor drips out. Both needles were now kept horizontal. One was connected to the flask filled with Ringer's solution. The flask was set on a tripod and kept 2 or 3 cm higher than the head of the cat. The height of the flask could be varied at will without the solution's producing a pressure rise in the fourth ventricle. The temperature of the solution was kept at 38°C with a flame. The fourth ventricle was now flushed at such a rate that 5 cm^3 solution flowed from the draining needle per minute. We know from experience that such a rate exerts practically no pressure rise on the brain. Flushing with Ringer's solution at pH 3 generally produced increased sweat excretion about 3 to 5 min after the beginning of flushing; this reached its peak 10 min after flushing, gradually decreasing and disappearing about 5 min after the flushing liquid was replaced with normal Ringer's solution. We could repeat flushing several times and observe almost the same results with each flushing. The temperature rise, vascular contraction in the earlobes and tachypnea were likewise observed. During 30 min of flushing, a maximum rise in temperature of 1.0°C /267 was observed which dropped off to normal within 1 hour. The control, in which flushing was done with normal Ringer's solution (pH 7.4), showed no effect on sweat excretion and body temperature. When an acidic flushing solution of pH lower than 3 is used, sweat excretion and a rise in temperature are apparent. The fa

farther pH drops below 3, the more intense the result. Regardless of the more or less distinct effect on sweat excretion, no such distinct change in respiration was observed as in the case of intraarterial injection. The distinct effect on sweat excretion and body temperature caused by the acidic solution raised the question of whether an alkaline shift in the medulla oblongata produced from the liquor causes an opposite effect on sweat excretion and body temperature. The following study is devoted to this problem. We placed the cat in the hot box, at a temerature of 50°C, and as soon as sweat excretion on the forepaws, a temperature rise and tachypnea were noted, we began to flush the fourth ventricle. Flushing with alkaline Ringer's solution (pH 9) was followed, as expected, by an inhibiting action on sweat excretion, tachypnea and the temperature rise due to the application of heat. During flushing, sweat excretion was completely suppressed, but several minutes after the alkaline solution was replaced with the normal Ringer's solution (pH 7.4), sweat excretion commenced again. Increased body temperature was likewise completely suppressed to normal with a steep dropoff, but as soon as the solution was replaced with normal Ringer's solution, temperature began to rise again.

In the control, in which flushing was done with normal Ringer's solution (pH 7.4), no effect on sweat excretion or the body temperature produced by the application of heat was observed. At a pH of more than 8.5, the flushing liquid inhibits perspiration and temperature rise. As pH increases, the inhibition of sweat excretion and the temperature rise becomes more and more pronounced. Tables 3 and 4 provide a better overview of the experimental results. It can be demonstrated that sweat excretion and body temperature are regulated chemically via the medulla oblongata as in the case of respiratory regulation in that a shift in hydrogen ion concentration in the liquor or carotid blood in the acidic direction produces excitation of the perspiration centers, and a shift in the alkaline direction produces inhibition. /269

TABLE 3. EXPERIMENT: FOURTH VENTRICLE FLUSHED WITH ACIDIC, NORMAL AND ALKALINE RINGER'S SOLUTIONS. CAT, WEIGHT 2470 g, MALE. AMBIENT TEMPERATURE 19-20°C

Reaction of flushing liquid		Before flushing	Flushed with acidic or alkaline Ringer's soln. (Min.)						Flushed with normal Ringer's solution (pH 7.4) (Min.)												Temperature rise, total perspiration
			5	10	15	20	25	30	35	40	45	50	55	60	70	80	90	100	110	120	
Acidic (ph 2.5)	Temp. in °C	38	38,2	38,4	38,5	38,7	38,7	38,8	38,8	38,7	38,7	38,6	38,4	38,4	38,2	38,2	38	37,9	38	38	+ 0.8° C.
	Perspiration in mg right	—	3	4	5	5	6	5	4	2	—	—	—	—	—	—	—	—	—	—	34
	Perspiration in mg left	—	2	5	6	5	5	5	3	2	—	—	—	—	—	—	—	—	—	—	33
Basic (pH 9)	Temp. in °C	38	38	38,1	38	38	38	38,1	38	38	37,9	38	38	38,1	38	38	38,1	38	38	38	—
	Perspiration in mg right	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Perspiration in mg left	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

TABLE 4. EXPERIMENT: FOURTH VENTRICLE FLUSHED WITH ALKALINE RINGER'S SOLUTION (pH 9), CAT HEATED IN BOX. CAT, WEIGHT 2890 g, MALE. AMBIENT TEMPERATURE 17-18°C

	Before heating	During heating (50° C)																	
		Flushed with normal Ringer's solution (pH 7.4) (Min.)						Flushed with alkaline Ringer's solution (pH 9) (Min.)						Flushed with normal Ringer's solution (pH 7.4) (Min.)					
		5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90
Temp. in °C	37,5	37,5	37,5	37,7	37,8	37,8	37,9	37,9	37,8	37,8	37,7	37,7	37,6	37,6	37,7	37,7	37,8	37,8	37,9
Perspiration in mg right	—	3	4	5	4	5	5	3	2	0	0	0	0	0	2	4	3	4	5
Perspiration in mg left	—	2	5	6	5	5	5	2	2	0	0	0	0	0	0	2	3	5	5

It can also be assumed that chemical control of the medullary perspiration center takes place without the involvement of the diencephalic center. The similar response of the perspiration center and the respiration center to a shift in reaction supports the idea that respiration, like sweat excretion, plays an important role in thermoregulation and that a causal relationship also exists between the two centers.

3. The Effect of Direct Reaction Modification at Various Points in the Medulla Oblongata upon Sweat Excretion and Body Temperature

The intimate relationship between the medulla oblongata and sweat excretion has already been demonstrated by means of classical experiments. In my experiments described above, I have assumed the medulla oblongata to be the subordinate center for sweat excretion, since the former reacts markedly to a shift in reaction without involvement of the diencephalon. However, our knowledge of the exact location of the medullary perspiration center is still extremely incomplete. I thus sought to make a few contributions in this direction. With regard to the center of vegetative functions in the medulla oblongata, the many pieces of evidence from experimental neurology make it appear very probable that the cells of the dorsal vagal nucleus are very important for vascular innervation and metabolic processes. Recently, Brugsch, Dresel and Lewy [6] have designated the dorsal vagal nucleus as the vegetative oblongata nucleus, since they found not only vagal cells in it but also sympathetic cells. With regard to the central regulation of sugar metabolism, they found that sugar (diabetic) puncture into the vegetative oblongata nucleus, when done into the sympathetic cells located in the posterior portion, increased the blood sugar level, whereas puncture into the vagal cells located in the posterior section caused a drop in blood sugar. Thus stimulation of the medulla oblongata can excite either the adrenal gland, through the sympathetic system, or the

pancreas, through the parasympathetic system, to increased activity. Their experiments primarily raised the question of whether the vegetative oblongata nucleus comes under consideration as the medullary perspiration center. The principal aim of the present series of studies is to determine whether and at what point the medulla oblongata reacts to the direct application of acid or alkali with sweat excretion. The method used is the following: A fine needle, its tip wrapped with cotton, was dipped in Ringer's /270 solutions of various pH and inserted into various areas of the medulla oblongata in order to directly alter the reaction and to study the resultant sweat excretion and temperature change. After the experiment, the animal was sacrificed, the medulla oblongata was removed and fixed in formalin solution, and the location of the puncture was determined by microscopic examination. In view of the fact that the vegetative oblongata nucleus is the central point of the efferent vegetative nerves, the action of direct acid or alkali application to this area was studied with particular care. Several anatomical remarks concerning the rhomboid fossa should be inserted here. In the caudal portion of the fossa, we note a rectangular field established by its slightly depressed location, the ala cinerea, under which the nucleus alae cinereae lies. The rostrale portion of the ala cinerea, particularly depressed, is called the fovea inferior. If, from the rostrale tip of the ala cinerea, we draw a perpendicular to the sulcus medianus, a triangular field is thereby delimited, the trigonum nervi hypoglossi, below which the nucleus of the n. hypoglossus lies. With regard to the size of the vegetative oblongata nucleus, Marburg [10] states that it extends laterally from the trigonum nervi hypoglossi as a slender column from the fovea inferior to the calamus scriptorius.

a) Direct Application of Acidic or Alkaline Ringer's Solution at the Level of the Fovea Inferior

Acidic Ringer's solution (pH 3) was applied at a depth of about 2 mm in all cases. The puncture was first made in the sulcus

medianus, without causing either sweat excretion or a temperature change in the process. The reaction is also always negative if the reaction of the applied solution is shifted in the acid direction. If it is applied directly into the fovea inferior, however, we always observe marked sweat excretion on the forepaws. In subsequent microscopic examination of the puncture point, it is found that the puncture was made into the cell group of the dorsal vagal nucleus or into an immediately adjacent location. The farther from this point in the medial or lateral directions application takes place, the less pronounced the sudorific effect. When positive results are obtained, it can always be demonstrated that the puncture was made precisely into the dorsal vagal nucleus or into immediately adjacent points. In the case of application into the glossopharyngeal nucleus, the result is always negative. /271 Sweat excretion is always linked with a moderate temperature drop, with individual fluctuations between 1.5 and 2°C, averaging 1.7°C. The reduced temperature is maintained for 50 to 70 min and slowly returns to the initial level in 3 or 4 hours. If the pH of the Ringer's solution is less than 6, sweat excretion and a drop in temperature are produced upon direct application into the dorsal vagal nucleus at the level of the fovea inferior. The farther the pH drops below 6, the more pronounced is its sudorific and temperature-reducing effect. As a control, I applied normal Ringer's solution (pH 7.4) into the fovea inferior and observed no sweat excretion, but a reduction of several tenths of a degree in temperature. An alkaline shift in the fovea inferior likewise causes no sweat excretion. As for temperature change, either no difference or a tendency toward a slight rise is observed. If alkaline Ringer's solution (pH 10) is applied to both sides of the fovea inferior and heat is applied in the hot box, profuse sweat excretion is markedly suppressed, but the rise in temperature is almost unaltered.

b) Direct Application of Acidic or Alkaline Ringer's Solution at the Level of the Ala Cinerea

Direct application was performed systematically from medial to lateral. If acidic Ringer's solution is applied no more than 1 mm laterally or medially from the ala cinerea, it always produces sweat excretion and temperature fluctuation. Microscopic findings in the positive cases always show that application has taken place in the dorsal vagal nucleus or close to it. The chemical stimulus affecting this section of the dorsal vagal core through an acid shift produces prompt, uniform sweat excretion on all four paws within a few minutes; it remains constant for more than 20 min and gradually disappears in 40 min as the acid effect wears off. The farther in front of the center of the ala cinerea toward the fovea inferior it is applied, the more profuse sweat excretion is, and the more posterior, toward the calamus scriptorius, it takes place, the smaller the quantity of perspiration. After just 20 or 30 min, the cat exhibits a rapid variation in temperature which persists for more than 1 hour and usually returns to normal in about 3 or 4 hours. When acidic solution, pH 3, is applied, a temperature drop of 1.5 to 2°C is /272 usually triggered by the section located anterior to the center of the ala cinerea and, in place of a decrease, an increase of 1.5 to 2.5°C is produced by the section located posterior to it. The farther from the dorsal vagal nucleus chemical stimulation occurs, the smaller its effect is. In contrast to the relatively prompt and pronounced effect of acidic application on sweat excretion and temperature variation, such an effect on respiration cannot be observed. It therefore appears questionable that stimulation of the actual center or reflective involvement of the diencephalic center is operant in sweat excretion as the result of chemical stimuli. The next task is to clarify this question. In order to eliminate the diencephalon, the peduncle is severed transversely after removal of the rear portion of the cerebellum. A drop in body temperature gradually occurs after

severing. These results are the same as those obtained with animals not operated on. This suggests an independent secondary center for sweat excretion and body temperature in the dorsal vagal nucleus.

While the dorsal vagal nucleus reacts very sensitively to an acid shift, producing perspiration and temperature change, it was found during the study that an alkaline shift acts differently on sweat excretion and temperature variation. The application of alkaline solution (pH 10) in sections of the dorsal vagal nucleus located in front of the center of the ala cinerea generally causes neither a perspiration reaction nor a temperature change, but causes temporary, pronounced suppression of the profuse excretion of perspiration upon insertion in the hot box. The temperature rise occurring in the latter case remained almost unchanged by the application of alkali, however. The portion of the dorsal vagal nucleus located posterior to the center of the ala cinerea reacts to alkaline application (pH 10) with a slight temperature rise and no sweat excretion. Alkaline application to the same section prior to or during insertion of the cat in the hot box produces almost no inhibition of the resultant profuse excretion of perspiration, but causes inhibition of the temperature rise. If the pH of the solution is higher than 8.5, the inhibition of sweat excretion and temperature rise always occurs. If it increases farther beyond 8.5, the result becomes more pronounced.

c) Application of Acidic or Alkaline Ringer's Solution at the Level of the Calamus Scriptorius

The direct application of acidic solution (pH 3) into the center line causes neither fever nor perspiration. If application takes place in the region located about 1 mm laterally from the /273
center line, however, immediate, uniform sweat excretion on the forepaws, a temperature rise with individual variation between 1.5°C and 2.5°C, and tachypnea set in. Sweat excretion occurs

relatively promptly, lasts 20 or 30 min, and then gradually disappears. The temperature rise sets in in about 30 min and gradually drops to the normal level again in 3 to 4 hours. Sweat excretion and rising temperature are caused by a hydrogen ion concentration slightly below pH 5.5. No inhibiting action on the profuse excretion of perspiration produced by the application of heat is caused by an alkaline shift at the same point, but the temperature rise is suppressed. The highest pH which inhibits the temperature rise is 8.5. When normal Ringer's solution (pH 7.4) is applied to the area located about 1 mm laterally from the center line at the level of the calamus scriptorius, only a temperature rise of 0.5 to 0.9°C occurs. The more laterally or lower the chemical stimulus is applied relative to this point, the slighter its effect is. The positive cases in which sweat secretion and a temperature rise due to acid application were observed involve stimulation of the caudal section of the dorsal vagal nucleus or immediately adjacent points. It is thus clear that the narrow zone extending diagonally from the fovea inferior toward the calamus scriptorius, corresponding histologically to the location of the dorsal vagal nucleus, has a considerable effect on body temperature and sweat excretion. If we compare the quantity of perspiration accompanying an acid shift in the fovea inferior with that in the region located 1 mm laterally from the center line at the level of the calamus scriptorius, the former is always about three times greater than the latter. The experimental findings have been tabulated to provide a better overview (see Tables 5 and 6).

The assumption of a special secondary, subordinate medullary perspiration center has thus been demonstrated experimentally to be correct. The dorsal vagal nucleus likewise represents a perspiration center, in addition to the center for sugar metabolism.

TABLE 5. RESULTS FROM THE DIRECT APPLICATION OF ACIDIC RINGER'S SOLUTION (pH 3) TO THE DORSAL VAGAL NUCLEUS. CAT, WEIGHT 3200 g, FEMALE. AMBIENT TEMPERATURE 18-20°C

Point of application		Before application	After application (Min)																	Temperature rise, total perspiration
			5	10	15	20	25	30	35	40	45	50	55	60	80	100	120	140	160	180	
Anterior half	Temp. in °C	37,6	37,5	37,4	37,2	37	37	36,8	36,7	36,5	36,3	36,2	36	36	36,1	36,4	36,8	37	37	37,4	−1.6
	Perspiration in mg right	—	2	5	7	7	6	6	4	3	2	—	—	—	—	—	—	—	—	—	42
	Perspiration in mg left	—	2	6	6	7	7	6	5	2	2	—	—	—	—	—	—	—	—	—	42
Posterior half	Temp. in °C	37,5	37,6	37,8	37,8	38	38,1	38,2	38,4	38,6	38,8	39	39,2	39,3	39,5	39,4	39,1	38,8	38,2	37,9	+2.0
	Perspiration in mg right	—	1	2	3	2	3	2	1	—	—	—	—	—	—	—	—	—	—	—	14
	Perspiration in mg left	—	1	3	2	3	2	2	2	—	—	—	—	—	—	—	—	—	—	—	15

Acidic solution was applied on the right in the anterior half of the dorsal vagal nucleus and on the left in the posterior half.

TABLE 6. BEHAVIOR OF TEMPERATURE VARIATION AND SWEAT EXCRETION AFTER THE DIRECT APPLICATION OF NORMAL, ACIDIC AND ALKALINE RINGER'S SOLUTIONS TO THE DORSAL VAGAL NUCLEUS

Point of application	pH of solution	Mean perspiration	Mean temperature variation	Number of trials
Anterior half	7.4	--	0.5°C drop	5
	3	{ right 42 mg, left 41 " }	1.7°C drop	6
	10	--	No change	6
Posterior half	7.4	--	0.7°C rise	5
	3	{ right 14 mg, left 14 " }	1.9°C rise	7
	10	--	0.3°C rise	5

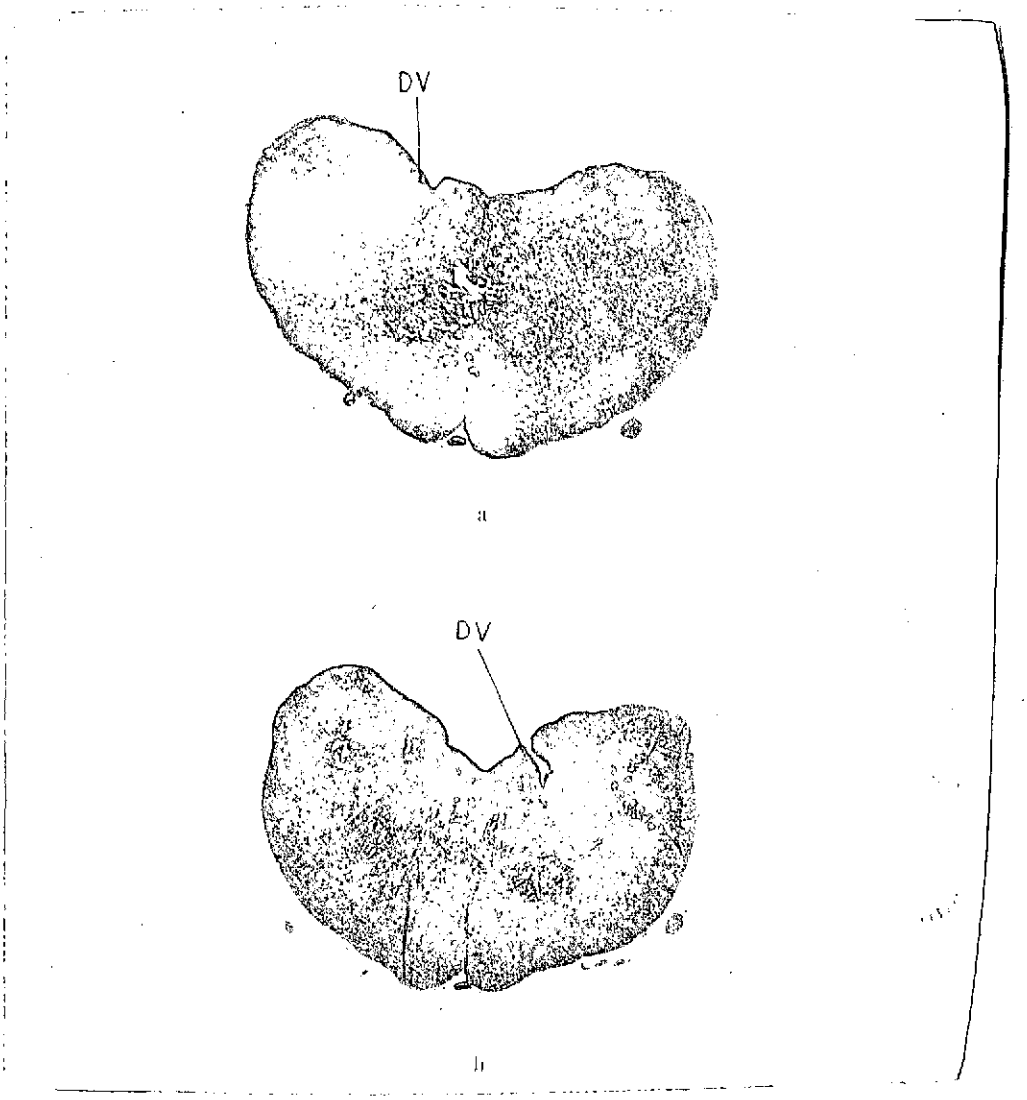

Fig. 5. Autopsy findings for the case shown in Table 5. a. Findings for the reaction to acid application with profuse sweat excretion and temperature drop. The figure shows the preparation located five sections caudally from the most frontal end of the dorsal vagal nucleus. The puncture, which penetrates rather perpendicularly from above into the dorsal vagal nucleus, is in the frontal half of the dorsal vagal nucleus. b. Findings for the reaction to acid application with slight sweat excretion and a temperature rise. The figure shows the preparation located seven sections frontally from the most caudal end of the dorsal vagal nucleus. The puncture, which penetrates somewhat obliquely from above into the dorsal vagal nucleus, is in the caudal half of the dorsal vagal nucleus (DV = dorsal vagal nucleus).

On the basis of their histological studies, though, Brugsch, Dresel and Lewy state that the dorsal vagal nucleus consists not only of vagal cells but also of sympathetic cells and that a stimulus applied to the vagal cells located in the anterior section is transmitted primarily via parasympathetic pathways to the pancreas and one applied to the sympathetic cells located in the /276
posterior section is transmitted via sympathetic pathways to the liver. Accordingly, it would not be impossible for the dorsal vagal nucleus to produce different types of sweat secretion. In my earlier article, I have already suggested that two forms of sweat secretion of different character are put in motion by two pathways, i.e. the sympathetic and parasympathetic systems. In order to check this assumption experimentally, I stimulated the entire surface of the dorsal vagal nucleus from the fovea inferior to the calamus scriptorius in a predetermined sequence. In extensive, detailed experiments, I was actually able to demonstrate that sweat excretion varies as a function of the point of stimulation: the same chemical stimulation produced profuse sweat excretion when applied to the anterior half of the dorsal vagal nucleus and very little when applied to the posterior half. The former was accompanied by a temperature drop and the latter by a temperature rise.

In order to analyze these results, it appears to be absolutely necessary to rule out the vegetative system. The following studies therefore involve the behavior of the dorsal vagal nucleus with an acid shift following elimination of the vegetative system by means of toxins, ergotoxine serving to block the sympathetic system and atropine to block the parasympathetic. Ergotoxine was injected subcutaneously 30 min prior to stimulation. Since the effect of atropine is very short-lived, the toxin was generally divided into two individual doses at intervals of 10 to 15 min before and after stimulation. This mode of time division has proven to be particularly effective. If atropine (4 mg per kg)

is injected to paralyze the parasympathetic endings, chemical stimulation by the application of acid in the anterior section of the dorsal vagal nucleus produces neither sweat excretion nor temperature reduction, as can be seen from Table 7, whereas the injection of ergotoxine does not inhibit the occurrence of either sweat excretion or temperature reduction. When the posterior section is stimulated, the behavior is quite the opposite. The injection of ergotoxine causes a depressor effect on sweat excretion and temperature increase. In contrast to the conspicuously inhibitory action of ergotoxine on the temperature rise and the slight sweat excretion, the injection of atropine had no effect on either. This fact made it justifiable to consider the dorsal vagal nucleus primarily to be a secondary sweat center and to assume it to have two functionally separate parts, one of which transmits the sudorific and temperature-reducing impulses to the /279
parasympathetic system and the other of which transmits sudorific and temperature-reducing excitation to the sympathetic system. These results further confirm the correctness of the assumption discussed in my earlier article [2] (see Tables 7 and 8).

4. The Effect of Thermal Stimulation of the Medulla Oblongata on Sweat Excretion and Body Temperature

Our knowledge concerning the relationship between the thermal factor and temperature regulation involves the effect on the corpus striatum almost exclusively, while analogous studies in the medullary vegetative centers are unfortunately nonexistent to date. The question now arises as to whether and to what extent thermal stimulation of the medulla oblongata affects the thermal budget and sweat excretion. The same apparatus that I employed in my earlier experiments was used to stimulate the medulla oblongata thermally. By systematically touching the entire surface of the rhomboid fossa point by point with a thermode tip through which hot or cold water flowed, it was possible to demarcate two regions which had sudorific responses to thermal

TABLE 7. RESULTS OF THE DIRECT APPLICATION OF ACIDIC RINGER'S SOLUTION (pH 3) INTO THE ANTERIOR HALF OF THE DORSAL VAGAL NUCLEUS AFTER SUBCUTANEOUS INJECTION OF ERGOTOXINE OR ATROPINE. CAT, WEIGHT 2780 g, MALE. AMBIENT TEMPERATURE 15-18°C

Type of toxin		Before application	After application (Min.) 5	10	15	20	25	30	35	40	45	50	55	60	80	100	120	140	160	180	Temperature rise, total perspiration
After ergotoxine injection (2 mg/kg)	Temp. in °C	37,7	37,6	37,5	37,2	37,1	37	37	36,9	36,8	36,5	36,4	36,2	36,2	36,2	36,5	36,8	37,2	37,5	37,5	— 1,5
	Perspiration in mg right	—	2	5	6	6	7	5	5	3	—	—	—	—	—	—	—	—	—	—	39
	Perspiration in mg left	—	3	4	6	5	6	7	5	2	—	—	—	—	—	—	—	—	—	—	38
After atropine injection (4 mg/kg)	Temp. in °C	37,6	37,5	37,6	37,5	37,5	37,5	37,4	37,4	37,4	37,3	37,3	37,2	37,2	37,3	37,4	37,5	37,6	37,7	37,6	— 0,1
	Perspiration in mg right	—	—	2	3	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	7
	Perspiration in mg left	—	—	2	2	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	6

First application of acid made on right, second on left.

TABLE 8. RESULTS OF DIRECT APPLICATION OF ACIDIC RINGER'S SOLUTION (pH 3) INTO THE POSTERIOR HALF OF THE DORSAL VAGAL NUCLEUS AFTER SUBCUTANEOUS INJECTION OF ATROPINE OR ERGOTOXINE. CAT, WEIGHT 3020 g, MALE. AMBIENT TEMPERATURE 13-16°C

Type of toxin		Before application	After application (Min.)																		Temperature rise, total perspiration
			5	10	15	20	25	30	35	40	45	50	55	60	80	100	120	140	160	180	
After atropine injection (4 mg/kg)	Temp. in °C	37,3	37,3	37,5	37,6	37,7	37,9	38	38,2	38,5	38,8	38,9	39	39	39	38,7	38,5	38,2	37,9	37,7	+1.7
	Perspiration in mg right	—	2	3	3	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	11
	Perspiration in mg left	—	2	3	2	3	2	—	—	—	—	—	—	—	—	—	—	—	—	—	12
After ergotoxine injection (2 mg/kg)	Temp. in °C	37,5	37,5	37,4	37,5	37,6	37,5	37,4	37,5	37,5	37,6	37,6	37,5	37,5	37,4	37,5	37,6	37,5	37,6	37,5	—
	Perspiration in mg right	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Perspiration in mg left	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

First application of acid made on right, second on left.

stimuli. The first region extended as a narrow zone from the center of the ala cinerea to the fovea inferior. When observed superficially, this corresponds to the frontal half of the dorsal vagal nucleus. It reacts to heat stimulation with profuse sweat excretion and a temperature drop, while cold stimulation has no effect. The more medially or laterally removed from this zone the heating occurs, the smaller the effect is. Even at relatively low temperatures, such as 42°C, one can obtain constant and appreciable sweat excretion from the zone outlined above. From another area which extends from the center of the ala cinerea to the calamus scriptorius, it is also possible to initiate sweat excretion, but it is very inconsistent and requires a higher temperature, above 50°C. The elimination of perspiration becomes promptly apparent, and the quantity rises steeply to a maximum and disappears after a slow decrease following the cessation of heat application. The second region is the posterior extension of the first region and is localized from the center of the ala cinerea to the calamus scriptorius. From this zone, it is possible to produce slight sweat excretion and a temperature increase through cold stimulation, but heat stimulation causes no sudorific or temperature-increasing effect in it. Outside this zone, no point can be found which has a sudorific effect in response to cold stimulation. /281 With regard to temperature change subsequent to thermal stimulation of the rhomboid fossa, it can be stated that it is primarily that point which has a sudorific effect in response to thermal stimuli which is related to the thermoregulatory zone. Thermal stimulation of other points proved to be ineffective. Heating of the anterior section of the dorsal vagal nucleus for 30 min caused a temperature drop with a steep curve, which returned to the initial level within 2 hours. The temperature drop accompanying 30 min of heating (50°C) is 1 to 1.3°C. On the other hand, cooling of the same point causes no temperature change. Thermal stimulation of the posterior half of the dorsal vagal nucleus proved to have the opposite effect. Thirty minutes of cooling (3°C) could be used to produce slight sweat excretion and a

temperature rise here, with individual variations between 1.2° and 1.7°C, but heating produced no results (see Table 9). The following study was again concerned with the behavior associated with thermal stimulation of the dorsal vagal nucleus after elimination of the vegetative system by means of toxins. Tables 10 and 11 each provide an example of the depressor action of atropine on profuse sweat excretion and temperature reduction resulting from the application of heat and the depressor action of ergotoxine on the slight excretion of sweat and rise in temperature due to the application of cold.

These observations generally agree with those by Brugsch, Dresel and Lewy, who were concerned with the significance of the dorsal vagal nucleus with respect to sugar regulation. Once the peduncle was severed to cut out the diencephalon, thermal stimulation proved to be just as effective as prior to severing. /282
This supports the idea that the central control of sweat excretion proceeds in the medulla oblongata without involvement of the diencephalon. The establishment of two physiologically different parts of the medullary perspiration center, one of which is of a sympathetic nature, the other of a parasympathetic nature, is reminiscent of the same system in the diencephalic center. Following the application of alkali in the dorsal vagal nucleus, subsequent thermal stimulation produces no sweat excretion or temperature variation.

5. The Effect of Electrical Stimulation of the Medulla Oblongata on Sweat Excretion and Body Temperature

Electrical stimulation has been used most frequently by experimentors as a method for stimulating sweat excretion from the medulla oblongata. Most authors who have covered this subject agree that the medulla oblongata, particularly the rhomboid fossa, is involved to a large degree in the central initiation of sweat excretion. Winkler [5] has confirmed that sweat excretion can be

TABLE 9. RESULTS OF THERMAL STIMULATION OF THE RHOMBOID FOSSA.
CAT, WEIGHT 2970 g, MALE. AMBIENT TEMPERATURE 15-18°C

Point of stimulation	Type of stimulation			Before stimulation	During stimulation (Min.) 5	10	15	20	25	30	After stimulation (Min.) 35	40	45	50	55	60	65	70	75	80	85	90	Temperature rise, total perspiration
Anterior of center of ala cinerea	Heat (50° C)	Temp.	in°C	37,5	37,5	37,2	37,1	37	36,8	36,5	36,2	36	36	36,1	36,3	36,5	36,7	36,8	37	37,2	37,5	37,4	— 1,5
		Perspiration in mg	right	—	3	6	7	6	6	5	2	—	—	—	—	—	—	—	—	—	—	—	34
			left	—	2	5	7	6	6	6	2	—	—	—	—	—	—	—	—	—	—	—	35
	Cold (3° C)	Temp.	in°C	37,5	37,5	37,5	37,5	37,5	37,5	37,5	37,4	37,5	37,6	37,5	37,6	37,5	37,5	37,6	37,5	37,4	37,5	37,6	—
		Perspiration in mg	right	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
			left	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Posterior of center of alae cineria	Heat (50° C)	Temp.	in°C	37,6	37,6	37,5	37,6	37,6	37,6	37,7	37,8	37,8	37,7	37,6	37,6	37,6	37,5	37,6	37,6	37,6	37,7	37,7	—
		Perspiration in mg	right	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
			left	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Cold (3° C)	Temp.	in°C	37,7	37,8	38	38,2	38,5	38,6	38,7	38,9	38,9	38,7	38,5	38,4	38,3	38,1	38	38	37,8	37,7	37,6	+1,2
		Perspiration in mg	right	—	2	2	2	2	3	1	—	—	—	—	—	—	—	—	—	—	—	—	12
			left	—	3	2	2	2	2	1	1	—	—	—	—	—	—	—	—	—	—	—	13

TABLE 10. RESULTS OF HEATING (50°C, 30 min) THE POINT LOCATED 1 mm ANTERIOR TO THE CENTER OF THE ALA CINEREA AFTER SUBCUTANEOUS INJECTION OF ERGOTOXINE OR ATROPINE. CAT, WEIGHT 2800 g, MALE. AMBIENT TEMPERATURE 17-20°C

Type of toxin	Perspiration in mg		Temperature variation in °C
	right	left	
After ergotoxine injection (2 mg/kg)	40	41	Drop of 1.3
After atropine injection (4 mg/kg)	4	5	Drop of 0.4

TABLE 11. RESULTS OF COOLING (3°C, 30 min) THE POINT LOCATED 1 mm POSTERIOR TO THE CENTER OF THE ALA CINEREA AFTER SUBCUTANEOUS INJECTION OF ATROPINE OR ERGOTOXINE. CAT, WEIGHT 2800 g, MALE. AMBIENT TEMPERATURE 15-18°C

Type of toxin	Perspiration in mg		Temperature variation in °C
	right	left	
After atropine injection (4 mg/kg)	14	13	Rise of 1.5
After ergotoxine injection (2 mg/kg)	--	--	No change

initiated on all four paws from anywhere on the surface of the rhomboid fossa by electrical stimulation. It has also been established by Munk [11] that when the medulla oblongata is stimulated electrically, all four paws perspire simultaneously, and he calls the medulla oblongata a "through station" for all perspiration nerves. Adamkiewicz [4] observed that cats continue to sweat on all four paws even 1 hour after death upon electrical stimulation of the medulla oblongata. Although it is rather

generally assumed that the medulla oblongata, particularly the base of the fourth ventricle, represents a point which induces perspiration upon electrical stimulation, there is still no agreement regarding precise localization. Systematic studies to outline the sudorific zone in the medulla oblongata by electrical stimulation are unfortunately not yet available. /283

My present series of experiments is devoted to clarifying the question of whether the entire rhomboid fossa has a uniform sudorific reaction to electrical stimulation, or whether a certain point on it reacts most distinctly. On the basis of the results of the preceding series of experiments, an attempt was made to obtain sweat excretion and temperature variation via that point which has a sudorific reaction to thermal stimulation. The anterior section of this zone, which spreads from the center of the ala cinerea to the fovea inferior, reacts to electrical stimulation with profuse sweat excretion and a rapid temperature drop, whereas the posterior extension of the same zone, i.e. that extending obliquely from the center of the ala cinerea to the calamus scriptorius, reacts to electrical stimulation with the same current with slight sweat excretion but with a temperature rise. Stimulation can be repeated three or four times at intervals of 2 hours with almost the same results. As soon as the first zone is touched with the pairs of electrodes, which were applied for 30 min, sweat excretion occurs promptly, increases with a steep curve, and drops off in a slow curve after cessation of the stimulation. The temperature curve drops steeply by an average of 1.3°C in 2 hours and returns gradually to normal. In contrast to the profuse sweat excretion and decreasing temperature curve, the second zone reacts to the same stimulus with slight sweat excretion and a temperature rise averaging 1.5°C. The quantity of sweat in this case is about 1/3 smaller than in the other. The temperature rise commences in about 30 min and drops to the original level in about 2 hours. Occasionally, a sudorific

TABLE 12. RESULTS OF ELECTRICALLY STIMULATING THE RHOMBOID FOSSA.
CAT, WEIGHT 3300 g, MALE, AMBIENT TEMPERATURE 20-22°C

Point of stimulation		Before stimulation	During stimulation (Min.)						After stimulation (Min.)												Temperature rise, total/ perspiration
			5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	
1 mm anterior to center of ala cinerea	Temp. in °C	37,9	37,8	37,7	37,5	37,3	37	36,9	36,8	36,9	36,9	37	37,1	37,2	37,3	37,4	37,5	37,5	37,7	37,8	— 1,1
	Perspiration in mg right	—	4	5	7	7	6	6	4	2	—	—	—	—	—	—	—	—	—	—	41
	Perspiration in mg left	—	3	6	7	6	7	6	3	2	—	—	—	—	—	—	—	—	—	—	40
1 mm posterior to center of ala cineria	Temp. in °C	37,8	37,8	38,1	38,3	38,5	38,6	38,8	39	39,2	39,1	39	38,8	38,7	38,5	38,2	38,3	38,2	38	38	+ 1,4
	Perspiration in mg right	—	2	3	2	2	3	2	—	—	—	—	—	—	—	—	—	—	—	—	14
	Perspiration in mg left	—	1	3	2	2	2	2	1	—	—	—	—	—	—	—	—	—	—	—	13

effect was obtained by stimulating other points, particularly the tuberculum cuneatum, the clava, or the point immediately below the obex, but excretion is inconstant and high current was required to produce it, sometimes accompanied by vigorous defensive movements. The perception of pain is probably involved in the induction of sweat excretion through the stimulation of such points. The results in this series of tests generally agree with those of the preceding one. I have now given further consideration to

TABLE 13. RESULTS OF ELECTRICAL STIMULATION (30 min) OF A POINT LOCATED 1 mm ANTERIOR TO THE CENTER OF THE ALA CINEREA FOLLOWING SUBCUTANEOUS INJECTION OF ERGOTOXINE OR ATROPINE. CAT, WEIGHT 3300 g, FEMALE. AMBIENT TEMPERATURE 20-22°C.

Type of toxin	Perspiration in mg		Temperature variation in °C
	right	left	
After ergotoxine injection (2 mg/kg)	45	44	Drop of 1.1
After atropine injection (4 mg/kg)	6	5	Drop of 0.2

TABLE 14. RESULTS OF ELECTRICAL STIMULATION (30 min) OF A POINT LOCATED 1 mm POSTERIOR TO THE CENTER OF THE ALA CINEREA FOLLOWING SUBCUTANEOUS INJECTION OF ATROPINE OR ERGOTOXINE. CAT, WEIGHT 2980 g, MALE. AMBIENT TEMPERATURE 19-21°C.

Type of toxin	Perspiration in mg		Temperature variation in °C
	right	left	
After atropine injection (4 mg/kg)	11	12	Rise of 1.3
After ergotoxine injection (2 mg/kg)	--	--	No change

whether stimulation of the actual medullary perspiration center, only, is involved in the excretion of perspiration due to electrical stimulation, or whether involvement of the diencephalon /285 occurs. In order to determine this, I attempted to separate the medulla oblongata from the peduncle. The result here was that both sudorific and temperature-varying effects remained almost unchanged by this operation. It is thus clear that sweat excretion can be attributed only to stimulation of the actual medullary perspiration center, and the diencephalon plays no role here. A systematic study was now made of behavior and body temperature upon pharmacological interruption of the neural pathways coming under consideration here, i.e. the sympathetic and parasympathetic systems. The slight sweat excretion and temperature rise which are suppressed by ergotoxine, which blocks peripheral excitation of the sympathetic system, are unaffected by atropine, however, which blocks peripheral excitation of the parasympathetic system. In contrast to this, atropine has a pronounced depressor effect on profuse sweat excretion, with temperature reduction, whereas ertotoxine produces no effects on these. If alkaline Ringer's /286 solution (pH 11) is applied in the dorsal vagal nucleus, we observe no sweat excretion or temperature variation upon subsequent electrical stimulation.

Discussion of Results

If we now summarize the results of this work, on the basis of all available data, giving consideration to what is known so far, we can produce the following picture for the physiological course of sweat excretion and elevated temperature. It is possible to cause a change in sweat excretion and in body temperature by shifting the reaction in the vicinity of the bulbar centers. Reaction shifts are produced hematogenically and from the liquor by intraarterial injection and flushing of the fourth ventricle with Ringer's solution exhibiting different pH values. Profuse

sweat excretion and a temperature rise were observed after the injection of acidic Ringer's solution into the carotid and flushing of the fourth ventricle with the same solution. In addition, an increase in breathing rate and heart beat rate were observed. The injection of alkaline Ringer's solution into the carotid and flushing of the fourth ventricle with it produced inhibition of the excretion of sweat and the rise in temperature due to the application of heat. In addition, a reduction in breathing and heart rates was observed. This makes it clear that chemical central regulation for sweat excretion and temperature variation proceeds in the bulbar centers via reaction shifts. The next goal was to answer the question of how and where the mechanism of chemical regulation proceeds. Systematic direct application of acidic Ringer's solution and alkaline solution within the entire extent of the base of the fourth ventricle, with a simultaneous check of the exposed point by histological examination, made it clear that only a stimulus affecting the dorsal vagal nucleus produces sweat excretion and temperature variation. Chemical stimulation by the application of acid to the anterior half of the dorsal vagal nucleus caused profuse sweat excretion, accompanied by a temperature drop, while slight sweat excretion with a temperature rise was obtained by stimulation of the posterior half. The quantity of sweat accompanying the former is about three times larger than that in the latter case. In addition to sweat excretion, a tendency toward a slight temperature rise was produced by application in the anterior half. Neither sweat excretion nor temperature variation was obtained by application in the posterior half. The assumption that the dorsal vagal nucleus is intimately related to thermoregulation and sweat excretion now has a confirmed experimental basis. On the basis of the findings that in spite of separation of the peduncle, stimulation affecting the dorsal vagal nucleus causes sweat excretion and temperature variation of almost the same intensity, we can also assume that the function of the dorsal vagal nucleus is performed independently of the diencephalic centers. Kraus' school has already demonstrated

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that the dorsal vagal nucleus represents a sugar center and that stimulation of it causes a reduction or rise in the blood sugar level. It is considered probable that the heat center is more extensive and that it is connected with the centers for vasomotor activity, sweat excretion and protein and carbohydrate metabolism processes. On the other hand, evidence of the extensive vegetative center in the diencephalon and in the medulla oblongata has caused the heat centers to be assigned to that area. Thus the question of central thermoregulation is included in the overall problem of the central regulation of vegetative functions. In addition to the significance of the dorsal vagal nucleus with respect to sugar regulation, that with respect to thermoregulatory processes is also taken into consideration, since it has not been ruled out that thermoregulatory impulses from the diencephalon may be transmitted via the dorsal vagal nucleus, along primarily parasympathetic pathways, to the lungs and the large visceral glands. My experimental results have not only confirmed this suspicion but have also provided the additional result that two different impulses come from the dorsal vagal nucleus, a temperature-increasing one and a temperature-reducing one, the first of which is transmitted by a sympathetic pathway and the second by a parasympathetic pathway to the reacting organs. The dorsal vagal nucleus has thereby also been demonstrated to be the medullary center for sweat excretion. A sudorific and temperature-reducing impulse comes from the anterior half of it and is transmitted via a parasympathetic pathway, whereas a different type of sudorific impulse and temperature-increasing excitation propagate from the posterior half and make their way via the sympathetic system. These physiologically different functions correspond to the already familiar anatomical assumption that the caudal part of the dorsal vagal nucleus consists of sympathetic cells and its anterior part, of vagal cells; similar behavior of the superordinate /288
perspiration center of the diencephalon is also compatible with this. These results provide an additional experimental basis for my earlier assumption that the sudorific impulses, viewed both

pharmacologically and physiologically, are transmitted not only by sympathetic but also parasympathetic pathways to the reacting organs. By thermally stimulating the entire area of the rhomboid fossa, I was able to mark off that region which extends as a narrow zone from the fovea inferior to the calamus scriptorius. This region corresponds approximately to the location of the dorsal vagal nucleus. The anterior section of this zone reacts to the application of heat with profuse sweat excretion and temperature reduction, whereas the posterior section responds to cold with slight sweat excretion and a temperature rise. In conjunction with facts already known, these results indicate that the temperature-reducing and sudorific impulse from the diencephalon produced by thermal stimulation is transmitted by a parasympathetic pathway to the anterior section of the dorsal vagal nucleus, whereas the temperature-increasing and sudorific impulse triggered by cold stimulation is transmitted to the posterior section of it by a sympathetic pathway. Accordingly, it is very probable that the dorsal vagal nucleus represents an intermediate station in the transmission of thermoregulatory and sudorific stimulation and can function independently, without involvement of the diencephalon. On the basis of the finding that when the dorsal vagal nucleus is stimulated on one side, sweat excretion on the paws occurs not only on the corresponding side but also uniformly on the opposite side, it appears justifiable to assume that the unilateral crossing of perspiration pathways already suspected occurs below the dorsal vagal nucleus (Fig. 2).

Summary /289

1. The injection of acidic Ringer's solution into the carotid and flushing of the fourth ventricle with the same solution produce appreciable sweat excretion and body temperature increases, in addition to an increase in breathing and heart rates; on the other hand, the injection of alkaline Ringer's solution and flushing

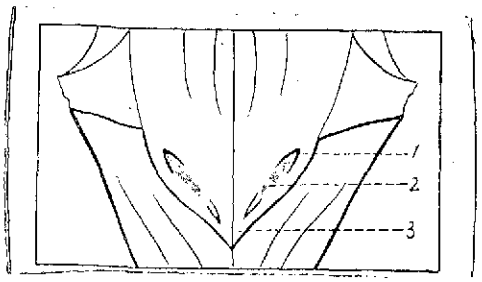

Fig. 2. Rhomboid fossa in the cat. 1. Fovea inferior. 2. Ala cinerea; 3. Calamus scriptorius. Shading indicates the zone which is connected with sweat excretion and temperature variation.

with it produce an inhibition of sweat excretion and temperature rise, in addition to a decrease in breathing and heart rate. The same results are also observed in animals whose peduncles are severed for the purpose of eliminating diencephalic function.

2. Temperature variation and a change in sweat excretion are also observed to accompany chemical stimulation of the dorsal vagal nucleus. Temperature is reduced, with profuse sweat excretion, from the anterior half of the dorsal vagal nucleus by the direct application of acidic Ringer's solution. These effects do not occur if the parasympathetic system is blocked with atropine. The direct application of acidic Ringer's solution into the caudal half of the dorsal vagal nucleus causes a temperature rise with slight sweat excretion, on the other hand. The occurrence of the two phenomena is entirely or almost entirely complicated by prior blockage with the injection of ergotoxine. While a temperature reduction is likewise achieved from the anterior half by the direct application of normal Ringer's solution, and a temperature rise from the posterior half, no sweat excretion is induced. Temperature variation is less intense and shorter-lived than that in the case of acid application, however. The application of alkali in both halves produces neither sweat excretion nor temperature variation and suppresses the sweat excretion and temperature rise which are caused by the application of heat.

3. It is also possible to outline, by thermal and electrical stimulation, that region which reacts with temperature variation and with sweat excretion. This zone spreads from the fovea

inferior as a narrow surface toward the calamus scriptorius and corresponds approximately to the location of the dorsal vagal nucleus. Thermal stimulation and electrical stimulation at the zone extending from the center of the ala cinerea to the fovea inferior causes a temperature drop with profuse sweat excretion. If the parasympathetic system is previously blocked with atropine, this effect can no longer be achieved. The zone spreading from the ala cinerea to the calamus scriptorius reacts to cold stimulation and electrical stimulation, however, with a temperature rise /290 and slight sweat excretion. Both are absent after the sympathetic system has been blocked with ergotoxine.

On the basis of the data available, we are justified in assuming that the area of the dorsal vagal nucleus represents a subordinate perspiration and heat center which consists of two parts, one of which is of a sympathetic nature and the other of a parasympathetic nature, and that these two parts react differently to chemical, thermal and electrical stimuli. The sudorific and temperature-varying function of the dorsal vagal nucleus occurs independently of the diencephalic centers.

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